

Prospective Comparison of Infective Endocarditis in Khon Kaen, Thailand and Rennes, France

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Abstract. Prospectively collected, contemporary data are lacking on how the features of infective endocarditis (IE) vary according to region. We, therefore, compared IE in Rennes, France and Khon Kaen, Thailand. Fifty-eight patients with confirmed IE were enrolled at each site during 2011 and 2012 using a common protocol. Compared with French patients, Thais had a lower median age (47 versus 70 years old; $P < 0.001$) and reported more animal contact (86% versus 21%; $P < 0.001$). There were more zoonotic infections among Thai than France patients (6 and 1 cases; $P = 0.017$) and fewer staphylococcal infections (4 versus 15 cases; $P = 0.011$). Underlying rheumatic heart disease was more prevalent in Thai than in French patients (31% and 4%; $P = 0.001$), whereas prosthetic heart valves were less prevalent (9% and 35%; $P = 0.001$). Our data strengthen previous observations that IE in the tropics has distinctive demographic characteristics, risk factors, and etiologies and underscore the need for improved prevention and control strategies.

INTRODUCTION

Infective endocarditis (IE) remains among the deadliest of infectious diseases, with up to one-third of patients dying within the first year of diagnosis.¹ Limited data suggest that the characteristics of IE in low-income countries differ from those in industrialized countries.^{1–3} Rheumatic heart disease (RHD) remains prevalent in poor countries,^{2,3} where therapeutic heart surgery is rarely available,² and zoonotic pathogens account for many cases of IE in patients with negative blood cultures.^{4–6}

The characteristics of IE in both the industrialized world and less-developed regions change over time.⁷ RHD is becoming rare in developed countries, whereas the number of patients who undergo cardiac and vascular surgery is increasing.⁷ The population at risk for IE now predominantly comprises elderly patients with valvular degenerative disease, prosthetic heart valves, or infections associated with healthcare procedures, such as hemodialysis.⁸ Economic development in low-income countries has brought changes in IE characteristics; degenerative valve disease and congenital heart disease have overtaken RHD as the major heart conditions underlying IE in urban areas, such as Beijing, China,⁹ which are more affluent than rural areas.

To get a contemporary picture of IE in different settings, we designed an investigation to compare the etiology and epidemiological characteristics of IE in a low-income tropical region with those in a high-income temperate one. We used standard case definitions, an identical study protocol, and identical case report forms to prospectively describe the characteristics of an identical number of IE patients in Khon Kaen, Thailand and Rennes, France enrolled over a period of approximately 1 year.

MATERIALS AND METHODS

Study sites and patients. Within a pre-existing IE study in Khon Kaen, Thailand, we recognized etiologic differences from published studies in high-income countries.^{8,10} In the final year of the study, we implemented the same protocol, including laboratory testing, in Rennes, France at a hospital that also had ongoing IE investigations. Patients with definite IE according to modified Duke criteria were enrolled between January and December of 2012 at the Department of Infectious Diseases, Center Hospitalier Universitaire Pontchaillou, Rennes, France, a referral center for IE and cardiac surgery with a population catchment area of 1 million inhabitants in Brittany, a region in western France. Using the same protocol, patients were enrolled between September 29, 2011 and December 21, 2012 at the Departments of Medicine and Cardiovascular Surgery, Faculty of Medicine, Khon Kaen University, a cardiac referral center for northeast Thailand. There were 58 patients with IE in Rennes during 2012, and all were included in this investigation. By design, we compared the patients in Rennes with Khon Kaen IE patients who had been enrolled through December of 2012 and included all patients who had been consecutively enrolled going back from December of 2012 until 58 patients were identified. Northeast Thailand is the poorest region of Thailand. The World Bank estimated that, for 2011, northeast Thailand had a per capita gross national product of \$2,256 compared with \$34,814 for Brittany in northwest France.¹¹

A transthoracic echocardiogram was performed on patients suspected of having IE, and consenting patients age 16 years old or older who met modified Duke criteria¹² for definite IE were enrolled. Underlying cardiac conditions were assessed by cardiologists on the basis of patients' medical records, histories, physical examinations, and echocardiographic findings. We administered a standard questionnaire to assess demographic characteristics, comorbid conditions, and animal exposures. The study was approved by the Rennes Institutional Review Board (IRB), the Khon Kaen University IRB, and the Centers for Disease Control and Prevention (CDC) IRB.

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Identification of causative bacteria. On admission to the hospital, three independent blood samples for culture over a period of no more than 90 minutes and an acute serum specimen were obtained. One month after admission, a convalescent serum specimen was obtained, and study patients were evaluated by a cardiologist. Acute and convalescent sera were collected from all patients, and heart tissue was collected from patients requiring surgery. Specimens from Khon Kaen patients were sent for diagnostic testing to the Emerging Tropical Infections Research Unit in Marseille, France, a reference center for the identification of pathogens causing IE.¹³ Specimens from Rennes were tested on site using the same assays. We tested acute and convalescent sera for antibodies to *Coxiella burnetii*, the etiologic agent of Q fever, and *Legionella pneumophila* by indirect immunofluorescence assay (IFA) as previously described.¹⁴ Q fever IE was defined as phase 1 immunoglobulin G (IgG) reciprocal titers > 800, and *L. pneumophila* IE was defined as total antibody reciprocal titers \geq 256 on either serum specimen.¹³ Bartonella IE was defined as IFA IgG antibody reciprocal titers of \geq 800 to *Bartonella quintana* or *B. henselae*. Specific antibodies to *Brucella melitensis* and *Mycoplasma pneumoniae* were detected using commercial immunoenzymatic antibody tests (*Brucella* antibody and Platelia *M. pneumoniae* IgM Kits, respectively (Bio-Rad, Marnes-la-Coquette, France), and reciprocal titers \geq 200 were considered positive. We extracted DNA from surgically excised heart valves (when available) using the QIAamp DNA Tissue Kit (QIAGEN, Courtaboeuf, France) as described by the manufacturer. We used previously described broad-spectrum polymerase chain reaction (PCR) primers, amplification, and sequencing conditions¹² to detect all bacteria (16S rRNA), all fungi (18S rRNA), *Staphylococcus aureus*, *mitis* and *gallolyticus* group streptococci, *Enterococcus faecalis*, *E. faecium*, *M. hominis*, *C. burnetii*, *Bartonella* sp. and *Tropheryma whippelii*.

Statistical methods. Median age was compared by the Mann-Whitney *U* test. Other demographic and clinical characteristics of Thai and French IE patients were compared by χ^2 test, and two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Patients. At each site, 58 patients with definite IE according to modified Duke criteria were prospectively enrolled. Most patients at each site were males, but other demographic and clinical characteristics differed markedly (Table 1). Compared with patients enrolled in France, those from Thailand

TABLE 1

Demographic and clinical characteristics of patients with IE in Khon Kaen, Thailand and Rennes, France

	Khon Kaen (N = 58)	Rennes (N = 58)	P value
Median age, years (range)	47 (18–75)	70 (17–86)	< 0.001
Male	72%	67%	0.69
Lives in rural area	91%	49%	< 0.001
Animal contact	86%	21%	< 0.001
Received antibiotics during the week before admission	71%	48%	0.01
Blood culture-positive	31%	79%	< 0.001
RHD	31%	4%	0.001
Prosthetic heart valve	9%	35%	0.001

TABLE 2

Categories of bacteria identified in IE patients in Khon Kaen, Thailand and Rennes, France

	Khon Kaen (N = 58)	Rennes (N = 58)	P (cases with identified etiology)	P (all)
Zoonotic bacteria	6	1	0.017	0.114
Streptococci*	19	27	1.00	0.184
Staphylococci	4	15	0.065	0.011
Other	6	8	1.00	0.777
Bacteria identified	35 (60%)	51 (88%)	Not applicable	0.001

*Not including *S. suis*.

were significantly younger, were more likely to report living in rural environments, and had more frequent animal contact from raising poultry, raising livestock, or keeping pets. Significantly more Thai patients received antibiotics during the week before admission, and blood culture positivity rates were significantly lower in Khon Kaen than in Rennes. RHD was the most common underlying heart condition in Thai patients (31%) but uncommon among French participants (4%; *P* = 0.001). In contrast, among French patients, having a prosthetic valve was the most common pre-disposing heart condition, with more than one-third (35%) having a prosthetic heart valve(s) compared with 9% of Thai patients (*P* \leq 0.001).

Heart valves involved. In Khon Kaen, the aortic valve was involved, either singly or combined, in 37 patients, the mitral valve was involved in 23 patients, and the tricuspid valve was involved in 6 patients. In Rennes, aortic involvement was also found in 37 patients, and mitral valve involvement was found in 23 patients. There were three cases of tricuspid valve involvement. Pulmonary valve IE was not diagnosed at either site.

Bacteriological findings (Table 2). Bacteria were identified in only 35 of 58 Khon Kaen patients (61%) compared with 51 of 58 patients in Rennes (88%; *P* = 0.001). Six Khon Kaen patients had IE caused by zoonotic bacteria: two cases of *Streptococcus suis* and one case each of *C. burnetii*, *Erysipelothrix rhusiopathiae*, *B. henselae*, and *Campylobacter fetus*. In Rennes, only one IE case was associated with a zoonotic pathogen (*C. burnetii*). Streptococcal infections were common; non-zoonotic *Streptococcus* species (i.e., not *S. suis*) were identified in 19 (33%) of 58 IE cases in Khon Kaen and 27 (47%) of 58 cases in Rennes. Only 4 staphylococcal infections were identified in Khon Kaen compared with 15 infections in Rennes.

DISCUSSION

By using a common protocol over a similar time period, our findings confirmed differences in IE between developed and developing countries suggested by previous studies conducted independently in diverse regions. Although Thailand is a middle-income nation, the study was conducted in the northeast, its most impoverished region. Thai patients with IE were much younger than French patients (median age of 47 versus 70 years), which is consistent with findings from previous studies showing that IE patients in developing countries are younger.^{1,2,15–18} Blood cultures were positive in 31% of Thai patients compared with 79% of French patients. One contributing factor may have been that significantly more Thai patients had received antibiotics in the week before hospital admission, but a low rate of positive blood cultures seems to be a characteristic of IE in many developing countries.^{1,2,15,16}

Thai case-patients were significantly more likely to have reported residing in rural areas and have had animal contact than their French counterparts, possibly explaining the greater proportion of zoonotic infections among Thai patients. Among cases with an etiologic agent identified, zoonotic bacteria accounted for 17% of cases in Khon Kaen but only 2% of cases in Rennes. Two cases from Khon Kaen were caused by *S. suis*, a bacterium most commonly acquired by consuming raw or undercooked pork or pig blood.¹⁹ Most reports of human *S. suis* cases have come from southeast Asia, where there is a high density of pigs,²⁰ but sporadic cases of IE caused by this pathogen have been reported from northern Europe and France.²¹ Other zoonotic bacteria, such as *C. burnetii* (the causative agent of Q fever) and *Bartonella* species, are important causes of IE in developing countries.^{4–6} In Algeria and Tunisia, *Bartonella* endocarditis accounts for 15% and 9.8% of all endocarditis, respectively.^{5,22}

Valvular conditions pre-disposing to IE also differed between the two groups of patients. A significantly smaller proportion of patients had prosthetic valve IE in Khon Kaen than in Rennes. The use of prosthetic valves among patients has increased dramatically in industrialized countries^{1,8} along with cases of IE caused by *S. aureus*.⁸ There were 15 cases of *S. aureus* IE among study participants in Rennes compared with 4 cases in Thailand ($P = 0.011$) (Table 2). In contrast, acute rheumatic fever and its chronic sequelae, RHD, have become rare in most affluent populations but remain common in many developing countries.^{23–25} Underlying RHD was found in 31% of Thai IE but only 4% of French IE ($P = 0.001$). In a review of studies in developing countries, RHD was the most common underlying heart disease, and it was found in a median of 63% of all IE cases.²³

There were limitations in this investigation that merit caution in interpreting the results. We only studied two sites over a 1-year period. Although our results alone cannot be generalized to other regions, the differences between the two sites were consistent with findings from previous studies conducted independently of each other in different locations. The poor blood culture yield in Khon Kaen could have resulted in our missing certain pathogens disproportionately, and therefore, the distribution of bacterial pathogens identified may not represent the true etiologic distribution. It is unlikely, however, that *S. aureus* infections were often missed, because only 9% of Thai patients had prosthetic heart valves, which predispose to IE caused by this bacterium. The training of study staff was not standardized across sites, which could have led to different interpretations of certain questions and may limit inferences. For example, rural versus urban residence was not specifically defined, and interviewers and patients may have had different interpretations. Some patients in both countries probably lived in suburban areas rather than either urban or rural zones.

Although other factors, such as climate, pathogen ecology, and other unmeasured exposures, may account for some differences, our data from a prospective study of 116 patients with confirmed IE strengthen the evidence from other investigations that IE in low-income countries differs in key ways from IE in the industrialized world. IE patients in the developing world are younger, often have underlying RHD, rarely have *S. aureus* infections related to prosthetic heart valves or medical procedures, and more frequently have IE caused by zoonotic microorganisms.

Like the World Health Organization's 17 neglected tropical diseases, IE in the tropics is a close companion of poverty. RHD now occurs almost exclusively in the developing world or disadvantaged populations of more affluent countries, such as in aboriginal peoples in Australia or Pacific Islanders in New Zealand.^{17,23,26} It is estimated that over 33,700 RHD-related IE cases occur each year in less-developed countries and that these lead to over 8,400 deaths.²³ These deaths can be prevented: RHD can be controlled by delivery of secondary prophylaxis to prevent recurrences of rheumatic fever.^{23,25} However, obtaining high-quality data on the disease burden of RHD and IE in the tropics is a necessary pre-requisite. In conclusion, IE in the tropics has distinctive demographic characteristics, risk factors, etiologies, and management problems and deserves more attention from the tropical medicine community.

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